PROPORTION AND FACTOR ASSOCIATED WITH TREATMENT DEFAULT AMONG TUBERCULOSIS PATIENTS IN SABAH FOR THE YEAR 2016 -2020

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UNIVERSITI SAINS MALAYSIA

2023

PROPORTION AND FACTOR ASSOCIATED WITH TREATMENT DEFAULT AMONG TUBERCULOSIS PATIENTS IN SABAH FOR THE YEAR 2016 -2020

by

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Research Project Report submitted in partial fulfilment of the requirements for the degree of Master of Public Health

MAY 2023

ACKNOWLEDGEMENTS

In the name of Allah S.W.T, the Most Gracious, the Most Compassionate, and the Most Merciful, whose blessings I have received have greatly facilitated my journey to this stage. Without the guidance and support of the Almighty, completing this dissertation would have been impossible.

I would like to express my heartfelt appreciation to Associate Professor Dr. Kamarul Imran Musa, Head of Department, Department of Community Medicine, Universiti Sains Malaysia (USM) for his invaluable contributions to this thesis. His insightful discussions and unwavering support, particularly during the research proposal presentation, have been instrumental in shaping the direction and quality of this work.

I would like to express my heartfelt gratitude to my supervisor, Dr. Noor Aman A. Hamid, and my co-supervisor, Associate Professor Dr. Nik Rosmawati Nik Hussein. The unwavering support, guidance, and expertise have been invaluable throughout my research journey. Along with the constructive feedback and insightful suggestions have greatly contributed to the quality of this thesis.

I extend my sincere appreciation to the member of the research team, Dr. Roddy Teo as my co-researcher, for his valuable input, rigorous evaluation, and helpful recommendations. His expertise and diverse perspectives have enriched my research and improved the overall quality of my work.

I am deeply grateful to both of my parents, for their endless love, encouragement, and sacrifices. Their unwavering belief in me and constant support have been the driving force behind my academic accomplishments. I am truly fortunate to have such wonderful role models in my life.

Lastly, I want to express my deepest gratitude to my colleagues and classmate who generously contributed their time, insights, and experiences to this study. Their involvement has been essential in shaping the findings and conclusions of this thesis.

I am indebted to all the individuals mentioned above, countless others who have played a part in my academic and personal growth. This thesis would not have been possible without their support, encouragement, and contributions.

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LIST OF ABBREVIATIONS

AOR	Adjusted Odd Ratio
CI	Confidence Interval
DM	Diabetes mellitus
DOSM	Department of Statistic Malaysia
EPTB	Extra Pulmonary Tuberculosis
HIV	Human Immunodeficiency Virus
MDR-TB	Multiple Drug Resistance Tuberculosis
MOH	Ministry of Health Malaysia
OR	Odd ratio
PTB	Pulmonary Tuberculosis
SDG	Sustainable Development Goal
TB	Tuberculosis
WHO	World Health Organization

LIST OF SYMBOLS

>	More than
<	Less than
≥	More than and equal to
≤	Less than and equal to
=	Equal to
%	Percentage
α	Alpha
β	Beta

ABSTRAK

Latar Belakang: TB, penyakit berjangkit yang ditularkan melalui udara, terus menjadi ancaman yang besar dalam komuniti dan merupakan fokus utama kebimbangan dalam kesihatan awam. Walaupun boleh dicegah dan dirawat, TB masih merupakan penyebab kematian akibat jangkitan kedua selepas COVID-19, menempati peringkat ke-13 dalam kalangan penyebab utama kematian. Menurut data daripada Laporan Tuberkulosis Global WHO, TB telah meragut 1.6 juta nyawa pada tahun 2021. Cabaran besar dalam pengurusan TB adalah ketidakmampuan untuk menamatkan rawatan dalam tempoh yang biasanya memakan masa selama enam bulan atau lebih. Pesakit yang gagal menamatkan rawatan TB akan manjadi sumber jangkitan di dalam komuniti dan menyumbang kepada kadar kematian yang tinggi, kadar kes ulangan yang meningkat, dan kerintangan terhadap rawatan ubat.

Objektif: Kajian ini bertujuan untuk menentukan peratusan terhenti rawatan TB, menerangkan dan menentukan faktor-faktor sosiodemografi, penyakit yang mendasari, ciri-ciri klinikal TB, dan gaya hidup yang berkaitan dengan terhenti rawatan di kalangan pesakit TB di Sabah dari tahun 2016 hingga 2020.

Kaedah: Satu kajian kes kawalan telah dijalankan pada bulan Mac 2023 dengan menggunakan data sekunder. Kes-kes yang layak (terhenti rawatan) dan kawalan (berjaya dirawat) telah dipilih melalui pensampelan rawak mudah. Data ini diperoleh daripada Sistem Pendaftaran TB Nasional, MyTB. Pengumpulan data adalah menggunakan borang proforma, yang kemudiannya dianalisis menggunakan perisian SPSS. Hubungan antara terhenti rawatan dengan pelbagai faktor, seperti petunjuk

sosio-demografi, gaya hidup, penyakit yang mendasari, dan ciri-ciri klinikal, telah dikaji dan dianalisis menggunakan regresi logistik mudah dan berganda.

Keputusan: Peratusan terhenti rawatan di kalangan pesakit TB di Sabah dari tahun 2016 hingga 2020 adalah 3.13%. Sejumlah 380 pesakit (190 kes dan 190 kawalan) telah dipilih dalam kajian ini. Dalam kumpulan kes, majoriti daripada mereka adalah lelaki (77.4%), pribumi Sabah (74.2%), warganegara Malaysia (86.3%), tinggal di kawasan luar bandar (63.2%), mempunyai pendidikan menengah sebagai tahap pendidikan tertinggi (41.6%), bukan pesakit kencing manis (96.8%), negatif HIV (98.4%), perokok (55.8%), didiagnosis dengan tuberkulosis paru-paru (93.7%), sputum AFB positif pada sapuan awal (73.7%), dan mempunyai lesi x-ray paru-paru yang minima (44.7%). Status kewarganegaraan (bukan warganegara Malaysia) dan status merokok (perokok) menunjukkan hubungan yang signifikan dengan kegagalan rawatan TB (aOR 0.423; 95% CI: 0.248, 0.719), dan (aOR 2.268; 95% CI: 1.492, 3.448).

Kesimpulan: Berdasarkan penemuan ini, kami berkesimpulan bahawa terhenti rawatan TB adalah berkaitan rapat dengan status bukan warganegara dan merokok.

KATA KUNCI: Tuberkulosis, cicir rawatan, faktor risiko

ABSTRACT

PROPORTION AND FACTOR ASSOCIATED WITH TREATMENT DEFAULT AMONG TUBERCULOSIS PATIENTS IN SABAH FOR THE YEAR 2016 -2020

Background: TB, an airborne communicable disease, continues to pose a significant threat in our community and is the primary focus of concern for public health. Despite being preventable and curable, TB remains the second leading infectious cause of death after COVID-19, ranking 13th among all causes of mortality. According to data from the WHO Global Tuberculosis Report, TB claimed the lives of 1.6 million individuals in 2021. A significant challenge in managing tuberculosis (TB) is the inability to successfully complete the extended treatment duration, which typically lasts for six months or more. The persistence of the infection source contributes to heightened mortality rates, increased relapse rates, and facilitates the emergence of drug-resistant strains.

Objective: This study aims to determine the proportion of treatment default, describe and determine sociodemographic, underlying disease, clinical characteristic and lifestyle factor associated with treatment default among tuberculosis patients in Sabah from year 2016 - 2020

Methodology: A case control study was carried out in March 2023 using secondary data. Eligible cases (treatment default) and control (treatment success) were selected through simple random sampling. The data was sourced from the National TB Registry, MyTB. Collection of data involved the use of a proforma form, which was later analysed using SPSS software. The association between treatment default and

various factors, such as socio-demographic indicators, lifestyle, comorbidities, and clinical characteristics, was examined and analysed using simple and multiple logistic regression.

Result: The proportion of treatment default among TB patients in Sabah from 2016 - 2020 was 3.13%. A total of 380 patients (190 cases and 190 controls) were selected in the study. Among cases group, majority of them were male (77.4%), local Sabahan (74.2%), Malaysian citizen (86.3%), lived in rural area (63.2%), received secondary education as highest education level (41.6%), non-diabetic (96.8%), HIV negative (98.4%), smoker (55.8%), diagnosed with pulmonary tuberculosis (93.7%), initial smear positive sputum AFB (73.7%), had minimal chest x-ray lesion (44.7%). Citizenship status (non-Malaysian citizen) and smoking status (smoker) and showed a significant association with TB treatment default (aOR 0.423; 95% CI: 0.248, 0.719), and (aOR 2.268; 95% CI: 1.492, 3.448) respectively.

Conclusion: Based on these findings, we reached the conclusion that default in treatment was linked to non-Malaysian citizen status and smoking.

KEYWORDS: Tuberculosis, treatment default, risk factor

CHAPTER 1

INTRODUCTION

1.1 Background

Tuberculosis (TB), caused by Mycobacterium Tuberculosis, is a highly contagious airborne illness and remains one of the primary causes of mortality attributed to a single pathogen (World Health Organization, 2022). Approximately 25% of the world's population is believed to have contracted TB, although the majority of individuals do not progress to active TB disease, and a portion of them naturally eliminate the infection. In 2021, it is estimated that around 10.6 million individuals worldwide contracted TB, with an incidence rate of 134 cases per 100,000 population. Approximately, there were 1.4 million TB deaths estimated among individuals who were HIV-negative in 2021, while 187,000 deaths were among those who were HIV-positive. Collectively, these figures amount to a total of 1.6 million deaths. In terms of geographical distribution, the South-East Asia regions reported the highest number of TB cases in 2021, with the proportion of 45% of all TB cases worldwide.

In Malaysia, for the year 2021 alone, there were 21, 727 TB cases reported at the national level, with an estimation of 64 TB cases reported per 100, 000 population. In 2021, the number of deaths reported due to TB were 2, 288 cases, with an estimation of 6.8 deaths per 100, 000 population. Sabah, located at the East Malaysia, recorded higher burden of TB cases. Sabah reportedly contributes to 20–30% of all Malaysia's TB cases while having only 10% of the nation's population. Despite the fact that TB rates have decreased during the previous ten years in other regions of the country, TB cases in Sabah remained high, with the number of cases reported increasing from 144 to 217 cases per 100,000 population (Goroh *et al.*, 2020). Immigrant contributes more than 24% of newly diagnosed patients in Sabah, as they were a large number of

foreign-born people coming to the state in view of its unique geographical location (Nissapatorn *et al.*, 2007).

TB typically affects the lung and other sites of the body, and its infection is categorised according to the infected site. This disease is preventable and curable with six months treatment regime. The 2030 End TB Strategy is one of the Sustainable Development Goals (SDG) indicator platforms. This strategy emphasises early detection and treatment of all people with TB. However, treatment default, which is among the primary difficulties in controlling TB, is recognized as a significant impediment towards the achievement of the Sustainable Development Goal (SDG). According to WHO, TB treatment default can be defined as a patient who experiences a disruption in their treatment for a duration of two consecutive months or longer (World Health Organization, 2013). In 2021, only 88% of TB patient in Malaysia completed TB treatment.

There are several implications of defaulting to TB treatment. For the system, non-compliance to TB treatment can increase the transmission of the infection, resulting in substantial and irreversible harm to the effectiveness of the TB control program. (Afshari *et al.*, 2020). For individual patient, treatment default may result in extended duration of illness, emergence of clinical complications, development of drug resistance, and death. (Kigozi *et al.*, 2017). The treatment cost for drug-resistant TB were 38 times higher on average compared to those for drug-susceptible TB cases. (Oh *et al.*, 2017). Those who default treatment would continue to become the source of TB transmission in the population hence burdening the TB control program (Alobu *et al.*, 2014).

Multiple risk factors were linked to TB treatment default, namely sociodemographic factor, underlying disease, clinical characteristic of TB infection and lifestyle factor. By understanding these factors, it would give better understanding on treatment default in a local setting, at the same time assist in TB control programs on enhancing compliance to treatment and increase treatment success towards the objective of achieving the 2030 end TB strategy goal (Slama *et al.*, 2013). In Malaysia, treatments for TB are given free of charge to citizens and non- citizens.

1.2 Statement Problem and Rationale

There are limited studies about TB treatment defaulters in Malaysia especially in Sabah. There is also little to no local studies on treatment default which may be influenced by local culture and beliefs of health practice. By identifying the associated factors, it covers the knowledge gap for TB treatment default and aids the state and district health office to improve effective measure of TB control and prevention measures. This study also provides essential information regarding high-risk group for default treatment. This help for implementing better strategy and treatment closed monitoring.

1.3 Research Question

1. What is the proportion of treatment default among tuberculosis patients in Sabah from 2016 - 2020?
2. What are the sociodemographic and clinical factors associated with treatment default among tuberculosis patients in Sabah from 2016 - 2020?

1.4 Objectives

1.4.1 General Objective

To study the proportion and associated factors with treatment default among tuberculosis patients in Sabah from 2016 - 2020.

1.4.2 Specific Objective

1. To determine the proportion of treatment default among tuberculosis patients in Sabah from 2016 - 2020.
2. To determine the sociodemographic and clinical factors associated with treatment default among tuberculosis patients in Sabah from 2016 - 2020.

1.5 Research Hypothesis

H1: There are associations between sociodemographic and clinical factors with treatment default among tuberculosis patients in Sabah from 2016 - 2020.

CHAPTER 2

LITERATURE REVIEW

2.1 Epidemiology of tuberculosis

As one of the contagious infectious diseases, TB survived over 70,000 years since ancient times. As one of the earliest known diseases to impact humans, TB remains a significant cause of mortality globally (Barberis *et al.*, 2017). Meantime, the global prevalence of TB has affected nearly 2 billion individuals, with approximately 10.4 million new TB cases reported each year. Globally, about one third of the world's total population are carriers of TB Bacillus and have high potential of developing active disease. TB has consistently posed a significant health burden worldwide in view of its infectious nature, pathogenicity, chronic progression and long-term treatment needed (Barberis *et al.*, 2017).

There are two sequential processes in TB, infection and active disease. In roughly 10% of patients infected with TB bacillus, an active disease might emerge at any time during their lives (Guler *et al.*, 2015). TB transmission occurs through droplet containing bacilli, and once it enters the lung, infection may occur based on a few factors. Such factors are frequency of contact with an individual who has infectious pulmonary TB, the extent of the contact, closeness of contact, amount and virulence of pathogen transferred, and susceptibility of the individual exposed. Healthy or non-immunocompromised persons develop T-cell immunity three to four weeks after infection, resulting in decreased intracellular development of the bacteria. Despite this, the bacteria can persist intracellularly initially without creating clinical signs. Immunological defence mechanisms lead to the formation of tuberculous granulomas. On the other hand, clinically apparent TB can develop quickly after infection, especially

in children, people with comorbidities or immunocompromised people and later will develop active TB disease. This type of TB is known as progressive primary TB, and is highly contagious (Suárez *et al.*, 2019).

TB clinical symptoms are various and it can affect any or all organs. The lungs are the most usually affected, and 50% of untreated patients die within five years (Guler *et al.*, 2015). The typical clinical manifestations of pulmonary TB comprise persistent cough, production of sputum, loss of appetite, weight loss, fever, night sweats, and haemoptysis. If an individual shows any of these signs, TB should be suspected, especially if they have had contact with a person infected with TB. Radiographic manifestations of TB can range from subtle infiltrates to significant bilateral changes, often with multiple cavities, which are characteristic features of the disease. The upper lobes of the lungs typically exhibit more pronounced changes. Differential diagnosis of cavitation involves considering other infections, as well as malignant and inflammatory lung conditions (Loddenkemper *et al.*, 2015). TB infection may also involve other organs other than the lung, such as lymph nodes, pleura, gut, genitourinary system, gastrointestinal tract, skin, joints and bones, meninges, and others, and this is characterised as Extra Pulmonary TB (EPTB). Among all possible types of TB infection, the most common type of TB is pulmonary tuberculosis (PTB), which has significant epidemiological implications due to its highly contagious nature (Guler *et al.*, 2015).

TB diagnosis involved laboratory investigation and chest radiography. In most developing countries, sputum smear microscopy using acid-fast staining with carbol fuschin solution is still one of the most common procedures for diagnosing TB. However, due to its lack of sensitivity which varies widely between 20 to 80%, other

diagnosis methods were also applied (Huang *et al.*, 2022). According to the Malaysia Ministry of Health Clinical Practice Guideline on TB Management 2021, a few other diagnostic modalities can be used to detect the presence of TB infection, including Lateral flow urine lipoarabinomannan assay (LF-LAM), Xpert MTB and Xpert nucleic acid amplification tests, and Eiken Tuberculosis Loop-mediated Isothermal Amplification Test (TB-LAMP). During the beginning stages of TB treatment, a mycobacterial culture is typically obtained to verify the existence of Mycobacterium tuberculosis and to rule out the possibility of drug-resistant TB. (Ministry of Health Malaysia, 2021).

The goals of treating TB are to achieve the patient's recovery from TB, prevent mortality caused by active TB or its long-term impacts, prevent TB recurrence, reduce TB transmission to others, and hinder the emergence of drug resistance acquired through treatment (Abuaku *et al.*, 2010). The standard treatment for TB consists of 2 months of quadruple therapy with isoniazid, rifampicin, ethambutol, and pyrazinamide followed directly by a further four months of rifampicin and isoniazid. For extrapulmonary TB, the treatment may sometimes require extended duration (Suárez *et al.*, 2019). The aim of TB treatment is treatment success, comprised of cured and completed treatment outcomes.

In 1991, WHO introduced the Directly Observed Treatment Short (DOTS) course strategy for global TB control. This strategy implements close monitoring treatment adherence and accomplishment. It’s also a measure to control and prevent TB drug resistance (Fogel, 2015). In Malaysia, seventy- five percent of patients are on this treatment regimen, while the remaining patients are on treatment for more than six

months using other drug combinations, either due to drug intolerance or treatment failure (Iyawoo, 2004).

2.2 Tuberculosis treatment default

TB treatment default poses a major threat to TB control programs worldwide. Drug resistance, increased treatment cost, and death are some significant implication of treatment default (Pardeshi, 2010). According to WHO, treatment default is defined as a TB patient who has interrupted treatment for two consecutive months or more (Ministry of Health Malaysia, 2021). Several studies have noted that the local population's adherence to TB treatment was significantly lower due to a lack of knowledge, attitude, and perception pertaining the disease, its transmission, and its treatment among TB patients. Furthermore, patients tend to neglect the treatment regimen by failing to complete the full course of treatment (Sakuntala *et al.*, 2021).

Ensuring strict adherence to TB treatment is essential for achieving successful treatment outcomes. Based on the 2021 WHO Global TB Report, the worldwide rate of TB treatment default remained constant at 6% between 2012 and 2019. Notably, there has been a significant increase in recent years in cases of treatment default, leading to adverse outcomes such as treatment failure, mortality, household and community transmission of the disease, and the emergence of drug-resistant strains (Jiang *et al.*, 2023).

2.3 Factors associated with TB treatment default

There are many factors associated with treatment default studied previously. A retrospective cohort study done in Brazil in 2010 using National Notifiable Disease

Information System showed men have a higher risk for treatment default with OR = 1.45 (95% CI: 1.29-1.62) (Garrido Mda *et al.*, 2012). This finding was similar to a study in Tajikistan in 2014 with men had high tendency to default treatment with OR = 1.40 (95% CI: 1.33-2.40) (Wohlleben *et al.*, 2017).

As for the age group, a study done in South Korea in 2012 showed people aged 35-49 years old are more prone to default treatment with OR = 1.09; 95% CI: 0.64-1.85 (Choi *et al.*, 2014). Another study done in Iran in 2005 showed those within age group of 35 - 44 years old are more likely to default treatment with OR = 1.40; 95% CI: 0.56-3.47 (Afshari *et al.*, 2020).

Education level has been shown to influence the risk of default treatment among TB patients. According to Garrido et al. (2012) in a study conducted in Brazil, illiterate people are highly likely to default treatment with OR = 1.35 (95% CI: 1.15-1.57). This finding is similar to the study done in India in 2000, which shows illiterate group of people have higher risk of default treatment with OR = 1.30 (95% CI: 0.80-2.10) (Santha *et al.*, 2002).

Furthermore, employment status has been shown to contribute to TB defaulter risk. For instance, a study in Estonia in 2009 indicated that unemployed status had a 3.5 times risk of default (OR = 3.53; 95% CI: 2.30-5.43) (Kliiman and Altraja, 2010). Another study in Kenya in 2005 reported similar results, in which unemployed people are 1.2 times more prone to default treatment (OR = 1.20; 95% CI: 0.71-2.04) (Muture *et al.*, 2011).

Study has indicated that citizenship status has been found to be linked with a higher likelihood of defaulting on TB treatment. In Kuwait, a study conducted in 2014 showed non-citizens are more likely to default TB compared to local citizen (OR = 2.4;

95% CI: 1.90-6.40) (Zhang *et al.*, 2014). As for residential area, a study done in Morocco in 2013 showed that patients live urban area are more likely to default TB treatment compared to patients live in rural area (OR = 2.8; 95% CI: 1.90-4.10) (Tachfouti *et al.*, 2013). Similar with the finding, a study done in Estonia in 2010 where TB patients in living area has 1.8 times risk of defaulting TB treatment compared to patients live in rural area (95% CI: 1.00-3.42) (Kliiman and Altraja, 2010).

Underlying medical illnesses also contribute as an associative factor for TB treatment default. People with diabetes mellitus have a higher risk of default treatment based on a study done in Kuwait in 2010 (Zhang *et al.*, 2014) and South Korea in 2012 (Choi *et al.*, 2014), both with OR = 1.60 (95% CI: 1.80-4.44) and OR = 1.56 (95% CI: 0.95-2.56), respectively. On the other hand, people with HIV had a 1.3 times higher risk of default treatment based on a study conducted in South Africa in 2012 (aOR 1.30; 95% CI: 1.09-1.44) (Kigozi *et al.*, 2017). Different study conducted in Kenya in 2017 also reported similar findings with aOR 1.56 (95% CI: 1.25-1.94) for the risk of defaulted TB (Muture *et al.*, 2011).

Smokers also possess a higher risk of default treatment based on a study done in South Korea in 2012. The study reported that those who smoke less than 1pack/day were more likely to default treatment with OR = 1.11 (95% CI: 0.63-1.94) (Choi *et al.*, 2014). Meanwhile, a study done in India in 2000 showed people who smoke were more likely to default treatment with OR = 2.10 (95% CI: 1.30-3.40) (Santha *et al.*, 2002).

For clinical characteristic of TB disease, a study done in Tajikistan in 2017 showed patients with sputum AFB smear positive have 1.15 times risk of defaulting TB treatment compared to smear negative TB patients (95% CI: 0.83-1.59) (Wohlleben *et al.*, 2017). Similar with the finding, a study done in Kenya in 2011 also found that

patients with smear positive sputum AFB were highly likely to default in TB treatment (OR=1.1; 95% CI: 0.83-1.24) (Muture *et al.*, 2011). For TB location, a study done in India in 2000 showed that patients with pulmonary TB had higher risk defaulting TB treatment compared to patients with extra pulmonary TB (OR = 2.8; 95% CI: 0.99 - 11.1) (Santha *et al.*, 2002).

2.4 Conceptual Framework

Figure 2.1 shows factors associated with default in treatment among tuberculosis patients. The factors include sociodemographic factors, lifestyle, clinical characteristics, and comorbidities. In sociodemographic, the factors studied were patient's age, gender, ethnicity, citizenship status, education level, and residential area. For underlying disease and lifestyle, among disease studied were diabetes mellitus, HIV and smoking. For TB clinical characteristic, factors studied were chest x-ray lesion, TB location, and AFB sputum smear. Due to limitation of secondary data, some factors were unable to be studied such as income status, underlying illness such as CKD, COPD, BCG scar, and adverse TB drug reaction

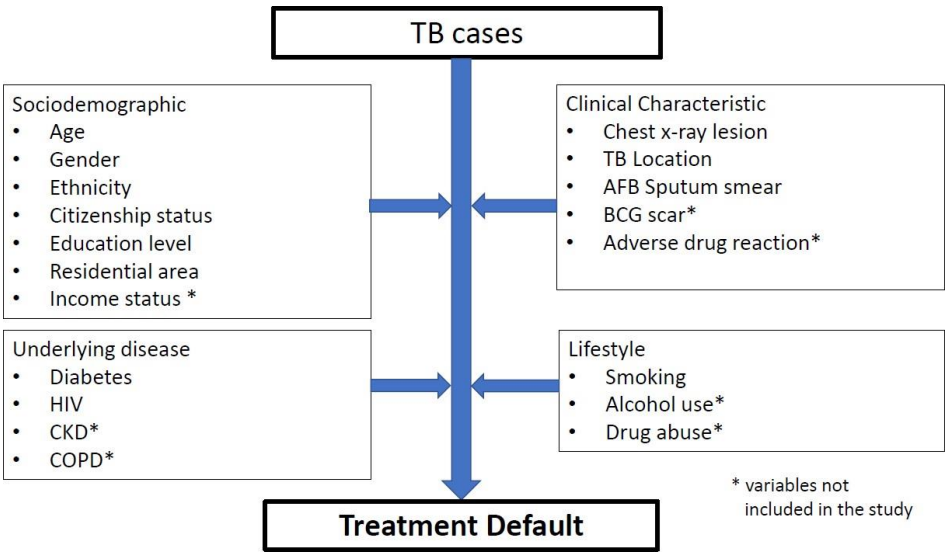

Figure 2.1: Conceptual framework of the study

CHAPTER 3

METHODOLOGY

3.1 Study Design

This study applied a retrospective record review with case-control design using anonymous data from the National TB surveillance database (MyTB). The MyTB data for the state of Sabah was used. Treatment default cases were identified so as to be able to understand the proportion of the cases. Next a case-control design was used to match the case (treatment default) against a control (completed treatment) with a 1:1 ratio. A case-control study design was selected due to the limited number of cases in the data set. All other treatment outcome including death, failed treatment and transferred out were excluded from sampling the sampling frame

3.2 Study Area

The study was conducted in Sabah. As the second largest state in Malaysia after Sarawak, Sabah shares its border with North Kalimantan on the south and the Philippines on the north. The geographical composition of the state encompasses a blend of mountainous terrains, coastal beaches, and lush tropical rainforests. As of 2021, Sabah's population comprises 3.4 million people. From the figure, 77.1% of the population is local citizens. For ethnicity, Local Sabahan comprised 88.9% of the total population, with the remaining 9.4% being Chinese and 1.7% other ethnicities. Most of the Sabah population are from the age group of 15-64 years old (68.3%), followed by the age group of 0-14 years old (25.8%) and the age group of more than 65 years old (5.9%). (DOSM, 2021).

3.3 Study Period

The study was conducted from January 2023 until June 2023.

3.4 Reference Population

All TB cases in Sabah reported in MyTB database from 2016 - 2020.

3.5 Source Population

All TB cases in Sabah reported in MyTB database from 2016 - 2020 that fulfill study criteria.

3.6 Inclusion Criteria

All TB cases in Sabah and reported in MyTB database from 2016 - 2020.

3.7 Exclusion Criteria

Incomplete data entry in MyTB of more than 20% which cannot be verified further, and patients with ongoing TB treatment were excluded.

3.8 Sample Size Calculation

Sample size was calculated using the formula of single proportion. For the first objective, the sample size was calculated to determine the proportion of TB treatment default among all TB patients in Sabah. The calculation was done using a web-based calculator (Arifin W. N., 2023). Conventionally the power of the study was set at 80% with $\alpha = 0.05$. Table 3.1 shows the sample size calculation for the first objective. The sample size was calculated, including an allowance of an additional 10% possibility of missing or incomplete data.

Table 3.1: Sample size calculation for the objective 1

α	Δ	P	N	n+10%	Reference
0.05	0.03	0.06	241	268	Liew *et al., 2015*
0.05	0.03	0.09	350	380	Arsad *et al.,* 2020

For objective 2, sample size was calculated with PS Software Version 3.1.6 using a comparison of two proportion formula.

Table 3.2: Sample size calculation for the objective 2

Risk factor	P0	P1	m	n (case)	n (control)	Total n+ 10%	Reference
Male	0.60	0.45	1	173	173	381	(Park *et al.*,2015)
Urban resident area	0.54	0.70	1	143	143	314	(Afshari *et al.*,2020)
Education level	0.55	0.70	1	162	162	356	(Park *et al.*,2015)
Non-citizen	0.84	0.70	1	141	141	310	(Zhang *et al.*,2014)
Diabetes mellitus	0.18	0.35	1	105	105	231	(Chiang *et al.*,2009)
HIV negative	0.22	0.40	1	102	102	224	(Afshari *et al.*,2020)
Chest x-ray finding	0.17	0.30	1	166	166	365	(Chang *et al.*,2004)
Smoking	0.50	0.35	1	169	169	372	(Park *et al.*,2015)

Table 3.2: continued.

Risk factor	P0	P1	m	n (case)	n (control)	Total n+ 10%*	Reference
Smear positive TB	0.39	0.55	1	152	152	334	(Wohlleben *et al*., 2017)
Pulmonary TB	0.70	0.55	1	162	162	356	(Chang *et al.*,2004)

P0 = proportion of exposure among control group based on literature review
P1 = estimated proportion of exposure among cases
Power of study = 80%
$\alpha = 0.05$
m = 1

Due to the potential for data entry mistakes, the final sample size was increased by 10% after computation for objective two. Utilising secondary data, this study was retrospectively conducted. Therefore, the drop-out calculation and important missing data were excluded. The biggest sample size determined as a result was 380.

3.9 Sampling Method and Subject Recruitment

For the case group, data were exported to Microsoft Excel, randomized and sorted. Simple random sampling was applied to select 190 patients for the case group. For the control group, selection was made from successful treatment outcomes (cured and completed treatment) documented in the MyTB dataset. Data were exported to Microsoft Excel, randomized and sorted. Simple random sampling was applied to select 190 patients for the control group. Case to control ratio was taken with a ratio of 1:1. Patients were matched on case to control group only.

3.10 Operational Definition

Treatment success refers to TB patient who are cured and have completed treatment. Treatment default was defined as TB patient who has interrupted treatment for two consecutive months or more.

3.11 Data Collection

This study involved data collection extracted from the National TB Surveillance database (MyTB), of which only cases from Sabah were used. All registered healthcare workers in charge of TB screening and treatment have access to key in the data to the database. The quality of the data is screened and checked for accuracy by a central manager on a monthly basis. Once the data has been verified, it is available to be used. The current dataset is only available until the year 2020. For research purposes, the data guardian released only anonymised data. The variables that are available on the database are Age, Gender, Citizenship status, Education level, Residential area, DM, HIV, Chest x-ray lesion, TB Location, AFB Sputum smear, and smoking history. A Proforma checklist was used to extract only relevant data for this study. Data was then be entered into Microsoft Excel and exported to SPSS software ver. 27 for analysis. Only the researchers have access to the data file.

3.12 Statistical Analysis

Data entered and analysed using SPSS ver. 27. Then, the data checked for any errors and cleaned. Preliminary data description was conducted to detect any missing values.

For objective 1, proportion of TB defaulter was calculated among success TB patient from the year 2016 - 2020. Data was presented in table.

For objective two, age for TB defaulted patients was presented in mean and SD. For socio-demographic, underlying disease, lifestyle factors, and tuberculosis clinical characteristics, descriptive statistics were conducted and presented as frequency (n) and percentage (%). Simple and multiple logistic regression were utilised to analyse each independent variable and the treatment outcome of default treatment and successful treatment. The independent variables that were analyzed were age, gender, citizenship status, ethnicity, residential area, education level, diabetes mellitus status, smoking status, TB location, AFB sputum smear, and chest x-ray lesion. Each independent variable was tested individually using simple logistic regression to see the association with the TB treatment outcome. Variables with *p*-value <0.25 and clinically significant were selected for multiple logistic regression. In this study, all independent variables were selected for multiple logistic regression analysis using forward likelihood ratio, backward likelihood ratio and enter method. Subsequently, a preliminary main effect model was obtained. Multicollinearity was checked using correlation matrix and standard error. Interaction between all the variables selected in the preliminary main effect model was also tested. Hence, the preliminary final model was obtained. Model fitness was checked using Hormer and Lemeshow goodness of fit test, and considered fit as the output value is near one. Besides the test, the classification table and area under the receiver operative curve (ROC) were also applied to determine model fitness. Finally, the final model was presented with an adjusted odd ratio and 95% confidence interval. A significant *p*-value was set at less than 0.05.

3.13 Study Flowchart

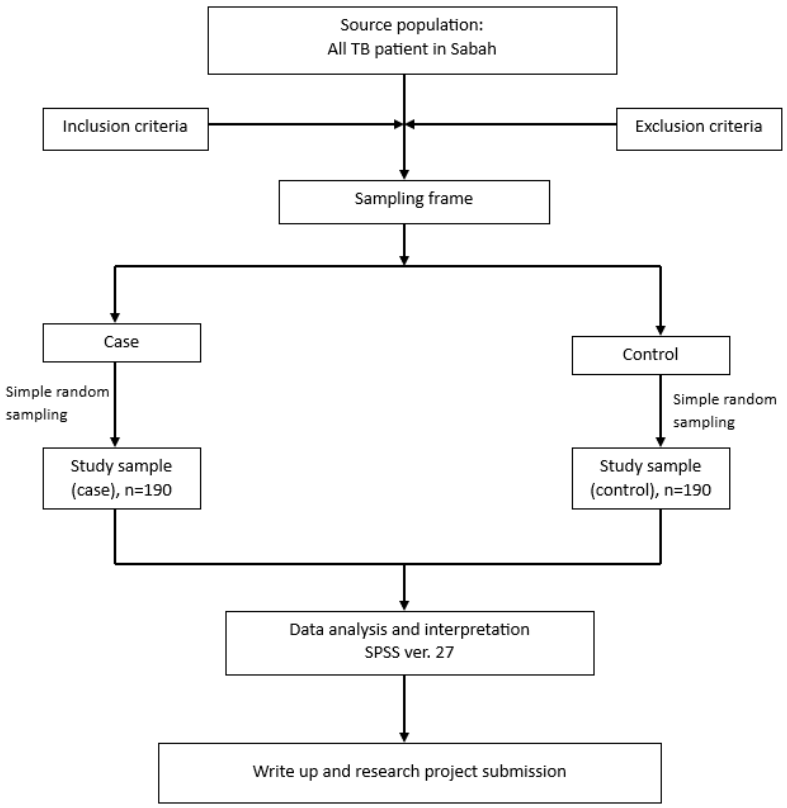

Figure 3.1: Study flow chart

3.14 Ethical Consideration

For data confidentiality, no personal individual was identified. Only anonymous information was analysed and entered into SPSS software. Data in the Excel sheet was encrypted as well as the laptop itself. Only researchers have access to the data. Data were presented as grouped data and were not identified by the responders individually. Laptop was stored in a safe and locked compartment.

This study also did not directly involve participant. Only anonymised data set were retrieved, thus protecting the privacy and confidentiality of the participants. The Principal Investigator and research team declared no conflict of interest in this study. The co-researcher, Dr Roddy Teo is the person incharge of the data management therefore, his experience and familiarity with the dataset is important to ensure accurate

management of the recorded data. To protect the integrity of the study, he was not involved in the data analysis and interpretation.

CHAPTER 4

RESULT

4.1 Proportion of treatment default among tuberculosis patients in Sabah from 2016 - 2020

From the year 2016 to 2020, they were a total 21,822 TB patients who were successfully treated and defaulted treatment. Table 4.1 shows the proportion of treatment default among tuberculosis patients in Sabah from 2016 to 2020. The total number of TB patients with treatment success were 21,138, and the total number of patients defaulted TB treatment were 684. From the figure, the 5-year average proportion of TB treatment default for the year 2016 to 2020 were 3.13% (95% CI: 2.90, 3.40).

Table 4.1: Proportion of treatment default among TB patients in Sabah from the year 2016 - 2020

Year	Treatment Success, n	Treatment Default, n	Proportion %	95% CI
2016	4,194	139	3.21	0.026, 0.037
2017	4,303	129	2.91	0.024, 0.034
2018	4,293	127	2.87	0.024, 0.037
2019	4,516	159	3.40	0.030, 0.041
2020	3,832	130	3.28	0.027, 0.038
Total	21,138	684	3.13	0.029, 0.034

4.2 Characteristic of TB default treatment patients in Sabah

From the total number of TB patients completed and defaulted treatment in Table 4.1, 760 patients were randomly selected as per calculated sample size. From the figure, 380 patients were treatment default patient categorised as case and 380 patients were

successfully treated categorised as control. From Table 4.2, the mean age for TB patients in Sabah was 37.6 years old (SD = 16.78).

For sociodemographic factor, majority of both case and control were from the age group of 20-39 years old with the proportion of 53.2% and 44.2% respectively. Majority of cases and controls were male, with 77.4% of cases and 65.3% of controls. Comparing of both cases and controls, male in case group were higher than male in control group.

In term of ethnicity, the local Sabahan was the most predominant ethnic in both case and control group. The proportion of local Sabahan ethnicity in case group is higher than control group (74.2% and 61.1%) respectively. For citizenship status, number of Malaysian citizens in case and control outnumbered non-Malaysian citizens. The proportion of Malaysian citizen in case group was 86.3% while in the control group the proportion was 72.1%. Most of the patients (71.6%) from control group live in the rural area, and from the case group, 63.2% patients live in the rural area.

For educational level, patients who attended at least secondary school were higher in both case and control group. They were 41.6% patients attended at least secondary school in case group compared to 36.8% patients attended at least secondary school from the control group. The least number of patients from both case and control group received tertiary education with the percentage of 5.8% and 10% respectively.

Two underlying illness analyzed in this study. Non-diabetic patients were predominant in both case and control groups. The number of non-diabetic patients were higher in case group compared to control group, with the proportion of 96.8% and 93.2% respectively. For HIV status, majority of patients from both case and control group were HIV negative. The number of HIV negative patients were higher in case

group (96.8%) compared to control group (93.2%). There were more smokers in the control group compared to case group. This was 55.8% and 35.3% respectively.

Among clinical characteristic of TB disease analysed in this study were TB location, AFB sputum smear and chest x-ray lesion. Most of the patients from case and control group were diagnosed as pulmonary TB with the proportion of 93.7% and 94.2% respectively. Initial sputum AFB smear shows each group has dominant number of AFB smear positive patients. Most of the patients from case and control group have minimal chest x-ray lesion with percentage of 44.7% and 45.3% respectively.

Table 4.2: Sociodemographic, underlying disease, clinical characteristic and lifestyle among of treatment default patients in Sabah from year 2016 – 2020

Variables	Mean (SD)	Successful Treatment, n=190	Default Treatment n=190
		n (%)	n (%)
Age	37.6 (16.78)		
Age group			
<20 years old		24 (12.6)	19 (10.0)
20 - 39 years old		84 (44.2)	101 (53.2)
40 - 59 years old		52 (27.4)	53 (27.9)
>59 years old		30 (15.8)	17 (8.9)
Gender			
Female		66 (34.7)	43 (22.6)
Male		124 (65.3)	147 (77.4)
Ethnicity			
Malay		2 (1.1)	4 (2.1)
Chinese		9 (4.7)	5 (2.6)
Indian		1 (0.5)	0 (0.0)

Table 4.2: continued

Variables	Mean (SD)	Successful Treatment, n=190	Default Treatment n=190
		n (%)	n (%)
Local Sabahan		116 (61.1)	141 (74.2)
Others		62 (32.6)	40 (21.1)
Citizenship			
Citizen		137 (72.1)	164 (86.3)
Non-Citizen		53 (27.9)	26 (13.7)
Residential area			
Urban		54 (28.4)	70 (36.8)
Rural		136 (71.6)	120 (63.2)
Educational level			
Tertiary		19 (10.0)	11 (5.8)
Secondary		70 (36.8)	79 (41.6)
Primary		35 (18.4)	37 (19.5)
No formal education		66 (34.7)	63 (33.2)
Diabetes mellitus			
No		177 (93.2)	184 (96.8)
Yes		13 (6.8)	6 (3.2)
HIV			
Negative		188 (98.9)	187 (98.4)
Positive		2 (1.1)	3 (1.6)
Smoking			
No		123 (64.7)	84 (44.2)
Yes		67 (35.3)	106 (55.8)
TB location			
Pulmonary		179 (94.2)	178 (93.7)
Extra pulmonary		11 (5.8)	12 (6.3)
AFB sputum smear			
Negative		49 (25.8)	50 (26.3)
Positive		141 (74.2)	140 (73.7)
Chest x-ray			
No lesion		11 (5.8)	12 (6.3)
Minimal lesion		86 (45.3)	85 (44.7)
Moderate lesion		81 (42.6)	82 (43.2)
Far advanced lesion		12 (6.3)	11 (5.8)

4.3 Factor associated with treatment default among tuberculosis patients in Sabah for year 2016 -2020

Simple and multiple logistic regression was utilized to identify factors associated with treatment default among TB patients. Simple logistic regression analysis is summarized in Table 4.3.

In simple logistic regression analysis, gender found to be a significant risk factor for TB treatment default. Male (Crude OR 1.82; 95% CI: 1.157,2.860; p=0.01) was significantly associated with TB treatment default compared to female. Citizenship also found to be a significant factor for TB treatment default. Non-citizen (Crude OR 0.41; 95% CI: 0.243,0.690; p=0.001) are less likely to default TB treatment compared to Malaysian citizen. Besides risk factor mentioned, ethnicity also has significant factor for TB treatment default. Other ethnicity comprises of Malay, Chinese, Indian, and other ethnicity has higher risk for defaulting TB treatment compared to local Sabahan (Crude OR 0.55; 95% CI:0.347,0.874; p=0.011). Lastly, smoking was also found to be statistically significant factor associated with defaulting TB treatment. Smokers were likely to default compared to non-smoker (Crude OR 2.32; 95% CI; 1.533, 3.501; p<0.001).

Table 4.3 Simple logistic regression of factor associated with treatment default among TB patients in Sabah for year 2016-2020

Variables	**Crude OR (95% CI)**	***p*-value**
Age group		
<20 years old	1	
20 - 39 years old	1.52 (0.779, 2.962)	0.220
40 - 60 years old	1.28 (0.631, 2.627)	0.487
>60 years old	0.72 (0.307, 1.669)	0.439
Gender		
Female	1	